

**REMARKS**

Claims 66-167 and 332-349 are all the claims pending in the application.

Drawings are objected to.

The disclosure is objected to because of some informalities.

Claims 66-69, 75, 82, 92-95, 101, 102, 332-335, 341-344 are objected to because of certain informalities.

Claims 66-107 and 332-349 are rejected under 35 U.S.C. 112, second paragraph as being indefinite.

Claims 92-94, 97, 100, 114, 341-343, and 346 are rejected under 35 U.S.C. 102(b) as being anticipated by WICHMANN et al.

Claims 92-96, 100 and 341-344 are rejected under 35 U.S.C. 102(b) as being anticipated by Kleim.

The Applicants traverse the rejections and request reconsideration.

**Objections to Drawings**

The Applicants respectfully submitted proposed drawing changes and request that these drawing amendments be considered.

The proposed changes should obviate the grounds raised for the objections of the drawings.

The Examiner notes that page 86 of the Specification refers to "Age Sections" of the MKB compartment which allegedly are not shown in the drawings. The Applicants respectfully submit that there are no specific reference to the alleged "Age Sections" on page 86. It is

believed all structural details necessary for the understanding of the **claimed invention** are shown in the drawings, satisfying the requirements.

### **Objection to the Specification**

The Applicants respectfully amend the Specification to provide a brief Description of Figure. 2b.

### **Claim Objections**

The Applicants respectfully amend the claims to overcome the grounds for the objections

### **Claim rejections under section 112**

The Examiner notes that the term realistic is indefinite. The Applicants further clarify the term as under. The Applicants concur with the Examiner in that the mathematical model provided in the Specification is an example of a realistic process model. The Applicants further clarify that a “realistic model/system” is one which allows practically useful (eg., clinically) prediction of disease/treatment process and outcome, based on practically achievable (measurable) data. A necessary consequence of such a definition is that the model structure and dynamics needs to closely mimic the structure and dynamics of a real physiological system. A corollary to that is a demand for the model’s parameters to correlate to practically measurable, or at least physiologically and clinically meaningful entities or observations.

Based on this a realistic model is one, i) whose structure is more similar to real physiological system’s structure, ii) whose dynamics reproduces more accurately the physiological system, and iii) whose parameters have more direct physiological meaning and preferably are more easy to measure. Needless to say, the three discussed aspects of realism are interrelated and depend one on another.

A skilled artisan would know the metes and bounds of the realistic model based on the Specification and the clarifications that are presently of record.

The claims have been amended to overcome the other grounds of rejection under 35 U.S.C. § 112, second paragraph.

**Section 102 rejections based on Wichmann and Kliem**

Claims 92 and 341 has been amended to specifically recite that the system is related to a human general patient. Both Wichmann and Kliem do not disclose a model for a human patient, and are therefore believed not to anticipate the rejected claims.

Claims 93-97, 100, 114 and 342-344 are dependant on the above claims and are allowable for the same reasons.

**CONCLUSION**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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23373

PATENT TRADEMARK OFFICE

Date: July 7, 2003

**APPENDIX**  
**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE CLAIMS:**

**The claims are amended as follows:**

66. (Amended) A system for modelling [Thrombopoietic] thrombopoietic lineage in an individual, said system comprising:

a [Thrombopoiesis] thrombopoiesis system model including a realistic process progression model, for cells involved in [Thrombopoiesis] thrombopoiesis, said progression model including multiplication and differentiation; and

a system model modifier, wherein said [Thrombopoiesis] thrombopoiesis system model is modified by the system model modifier based on parameters specific to the individual.

67. (Amended) The system of claim 66 wherein the system model [incorporates] comprises a realistic progression of cells involved in diseased [Thrombopoiesis] thrombopoiesis.

68. (Amended) The system of claim 67 wherein diseased [Thrombopoiesis] thrombopoiesis includes [Thrombocytopenia]thrombocytopenia.

69. (Amended) The system of claim 67 wherein the system model [incorporates] comprises effects of at least one drug in the realistic progression of cells involved in [Thrombopoiesis] thrombopoiesis.

70. (Amended) The system of claim 69 wherein said at least one drug is thrombopoietin [Thrombopoietin] (TPO).

71. (Amended) The system of claim 67 wherein said process model [imitates] is adapted to imitate a course of the individual's bone marrow progression, peripheral platelet counts and TPO concentration changes.

72. (Amended) The system of claim 67, wherein said process model [incorporates] comprises cell-suppressive treatment effects and effects of administration of TPO to [the] a patient.

73. (Amended) The system of claim 72, wherein said cell-suppressive treatment [can be] is chemotherapy.

75. (Amended) The system of claim 74 wherein said compartments include:  
a stem cell (SC) compartment that [comprises] is capable of modeling bone marrow haemopoietic progenitors that have an ability to differentiate into more than one cell line wherein cells in the stem cell compartment proliferate, mature and differentiate into one of megakaryocyte progenitors and new stem cells;

a colony forming units - megakaryocytes (CFU-Meg) compartment [, wherein the] that is capable of modeling megakaryocyte progenitors [get] getting committed as a megakaryocyte line and [spend] spending some time multiplying and maturing;

a megakaryoblast (MKB) compartment [, which] that is capable of modeling receiving of [ receives the] cells from CFU-Meg, wherein the cells in the MKB compartment have lost their ability to proliferate but are not mature to release platelets;

[a] an MK16 compartment [, which receives cell] that is capable of modeling receiving of cells from the MKB compartment, wherein a subset of cells in the MK16 compartment release platelets at a constant rate until [they] the subset of cells exhaust their capacity and are disintegrated and a second subset of cells do not release platelets but continue with endomitosis;

[a] an MK32 compartment that is capable of modeling receiving of [receives] the second subset of cells from the MK16 compartment, wherein a subset of cells in this compartment release platelets and a second subset of cells do not release platelets but continue with endomitosis;

[a] an MK64 compartment that [receives] is capable of modeling receiving of the second subset of cells from the MK32 compartment wherein a subset of cells in this compartment release platelets and a second subset of cells do not release platelets but continue with endomitosis;

[a] an MK128 compartment that [receives] is capable of modeling receiving of the second subset of cells from the MK64 compartment wherein a subset of cells in this compartment release platelets;

a platelets (PL) compartment.

76. (Amended) The system of claim 75 wherein the process model is capable of considering an effect of apoptosis [is included] with an overall effect of cell proliferation in giving rise to an amplification of cell numbers in a corresponding compartment.

77. (Amended) The system of claim 75 wherein the process model further [incorporates] comprises the effects of TPO on the SC, CFU-Meg and MKB compartments.

81. (Amended) The system of claim 77, wherein [the] a transit time of a cell is same in all platelet releasing compartments and the transit time of a cell of the SC, CFU-Meg and MKB compartments are functions of micro-environmental conditions.

82. (Amended) The system of claim 81 wherein in the SC compartment when the TPO concentration is above the threshold, the transit time of a cell is shortened based on the dose.

83. (Amended) The system of claim 81 wherein in the CFU-Meg and MKB, the transit time of a cell is solely based on TPO concentration.

91. (Amended) The system of claim 66, wherein said model is capable of being used for recommending an optimal treatment protocol, wherein said system further comprises:  
a plurality of treatment protocols; and

a selector to select an optimal treatment protocol from said plurality of treatment protocols based on the modified system model.

92. (Amended) A system for modelling [Thrombopoietic] thrombopoietic lineage in a general human patient, said system comprising a [Thrombopoiesis] thrombopoiesis system model including a realistic process model for cells involved in [Thrombopoiesis] thrombopoiesis.

93. (Amended) The system of claim 92 wherein the system model [incorporates] comprises a realistic progression of cells involved in diseased [Thrombopoiesis] thrombopoiesis.

94. (Amended) The system of claim 93 wherein diseased [Thrombopoiesis] thrombopoiesis includes [Thrombocytopenia]thrombocytopenia.

95. (Amended) The system of claim 93 wherein the system model [incorporates] comprises effects of at least one drug in the realistic progression of cells involved in [Thrombopoiesis] thrombopoiesis.

96. (Amended) The system of claim 95 wherein said at least one drug is [Thrombopoietin] thrombopoietin (TPO).

97. (Amended) The system of claim 93 wherein said process model [imitates] is adapted to imitate a course of the patient's bone marrow progression, peripheral platelet counts and TPO concentration changes.

98. (Amended) The system of claim 93, wherein said process model [incorporates] comprises cell-suppressive treatment effects and administration of TPO to the patient.

101. (Amended) The system of claim 100 wherein said compartments include:  
a stem cell (SC) compartment that [comprises] is capable of modeling bone marrow hemopoietic progenitors that have an ability to differentiate into more than one cell line wherein cells in the stem cell compartment proliferate, mature and differentiate into one of megakaryocyte progenitors and new stem cells;

a colony forming units - megakaryocytes (CFU-Meg) compartment [, wherein the] that is capable of modeling megakaryocyte progenitors [get] getting committed as a megakaryocyte line and [spend] spending some time multiplying and maturing;  
[a] an MK16 compartment [, which receives cell] that is capable of modeling receiving of cells from the MKB compartment, wherein a subset of cells in the MK16 compartment release platelets at a constant rate until [they] the subset of cells exhaust their capacity and are disintegrated and a second subset of cells do not release platelets but continue with endomitosis;  
[a] an MK32 compartment that is capable of modeling receiving of [receives] the second subset of cells from the MK16 compartment, wherein a subset of cells in this compartment

release platelets and a second subset of cells do not release platelets but continue with endomitosis;

[a] an MK64 compartment that [receives] is capable of modeling receiving of the second subset of cells from the MK32 compartment wherein a subset of cells in this compartment release platelets and a second subset of cells do not release platelets but continue with endomitosis;

[a] an MK128 compartment that [receives] is capable of modeling receiving of the second subset of cells from the MK64 compartment wherein a subset of cells in this compartment release platelets;

a platelets (PL) compartment.

102. (Amended) The system of claim 101 wherein the process model is capable of considering an effect of apoptosis [is included] with an overall effect of cell proliferation in giving rise to an amplification of cell numbers in a corresponding compartment.

103. (Amended) The system of claim 101 wherein the process model further [incorporates] comprises the effects of TPO on the SC, CFU-Meg and MKB compartments.

107. (Amended) The system of claim 103, wherein [the] a transit time of a cell is same in all platelet releasing compartments and the transit time of a cell of the SC, CFU-Meg and MKB compartments are functions of micro-environmental conditions.

108. (Amended) The system of claim 107 wherein in the SC compartment when the TPO concentration is above the threshold, the transit time of a cell is shortened based on the dose.

109. (Amended) The system of claim 107 wherein in the CFU-Meg and MKB, the transit time of a cell is solely based on TPO concentration.

117. (Amended) The system of claim 92, wherein said model is capable of being used for recommending an optimal treatment protocol, wherein said system further comprises:  
a plurality of treatment protocols; and  
a selector to select an optimal treatment protocol from said plurality of treatment protocols based on the modified system model.

332. A method for modelling [Thrombopoietic] thrombopoietic lineage in an individual, said method comprising:  
realistically modelling a process to create a process model for cells involved in [Thrombopoiesis] thrombopoiesis; and  
modifying the process model based on parameters specific to the individual.

333. (Amended) The method of claim 332 wherein a realistic progression of cells involved [indiseased Thrombopoiesis] in diseased thrombopoiesis is incorporated in the process model.

334. (Amended) The method of claim 333 wherein diseased [Thrombopoiesis] thrombopoiesis includes [Thrombocytopenia]thrombocytopenia.

335. (Amended) The method of claim 333 wherein effects of at least one drug in the realistic progression of cells involved in [Thrombopoiesis] thrombopoiesis is incorporated.

336. (Amended) The method of claim 335 wherein said at least one drug is [Thrombopoietin] thrombopoietin (TPO).

338. (Amended) The method of claim 333, wherein said process model [incorporates] comprises cell-suppressive treatment effects and administration of TPO to [the] a patient.

341. (Amended) A method for modelling [Thrombopoietic] thrombopoietic lineage in a general human patient, said method comprising:

realistically modelling a process to create a process model for cells involved in [Thrombopoiesis] thrombopoiesis.

342. (Amended) The method of claim 341 wherein a realistic progression of cells involved [indiseased Thrombopoiesis] in diseased thrombopoiesis is incorporated in the process model.

343. (Amended) The method of claim 342 wherein diseased [Thrombopoiesis]  
thrombopoiesis includes [Thrombocytopenia]thrombocytopenia.

344. (Amended) The method of claim 342 wherein effects of at least one drug in the  
realistic progression of cells involved in [Thrombopoiesis] thrombopoiesis is incorporated.

345. (Amended) The method of claim 344 wherein said at least one drug is  
[Thrombopoietin] thrombopoietin (TPO).

347. (Amended) The method of claim 342, wherein said process model [incorporates]  
comprises cell-suppressive treatment effects and administration of TPO to the patient.



SIMULATIONS SHOWING THAT IF THE PROTOCOL IS PRE-CALCULATED THEN A SIMILAR OR A HIGHER EFFICACY CAN BE OBTAINED USING 4-FOLD REDUCED TOTAL DOSE OF TPO.

TPO USE IN HEALTHY DONORS:

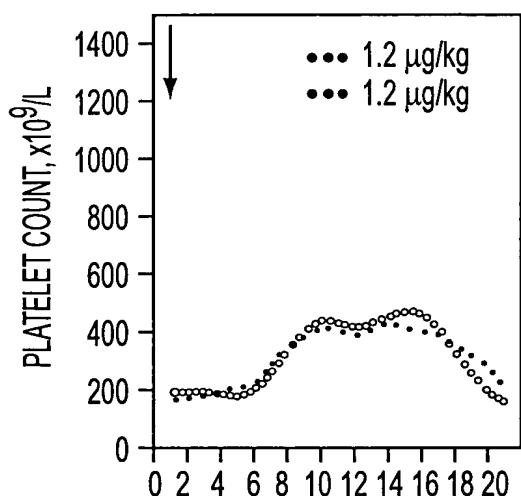


FIG. 8A

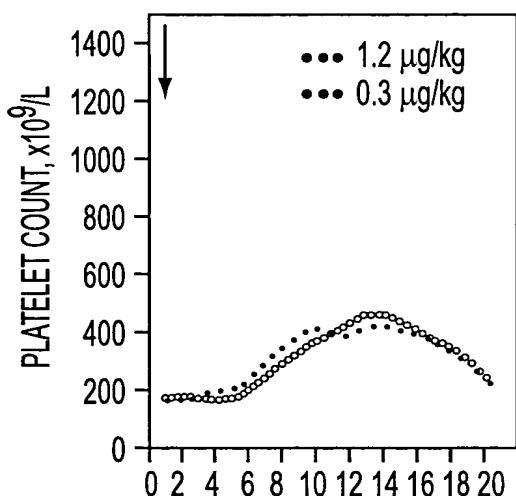


FIG. 8B

FIG. 8 TPO GIVEN TO HEALTHY DONORS- RESULTS OF TPO CLINICAL TRIALS FROM RECENT RESEARCH ON HEALTHY PLATELET DONORS, AS COMPARED TO OUR COMPUTER SIMULATION RESULTS. ARROWS INDICATE THE START OF TPO TREATMENT. (A) COMPARISON OF EXPERIMENTAL DATA FROM PUBLISHED ARTICLES<sup>1</sup> (BLACK) AND OUR MODEL SIMULATION (GREEN), IN BOTH TPO WAS GIVEN AS A SINGLE IV DOSE OF 1.2  $\mu$ g/kg ON DAY 0. (B) COMPARISON OF THE SAME EXPERIMENTAL DATA (BLACK) AND OUR PROPOSED TPO ADMINISTRATION PROTOCOL; THE TOTAL DOSE IN THE SIMULATED PROTOCOL WAS 0.3  $\mu$ g/kg (BLUE).

TPO USE IN PATIENTS RECEIVING CHEMOTHERAPY:

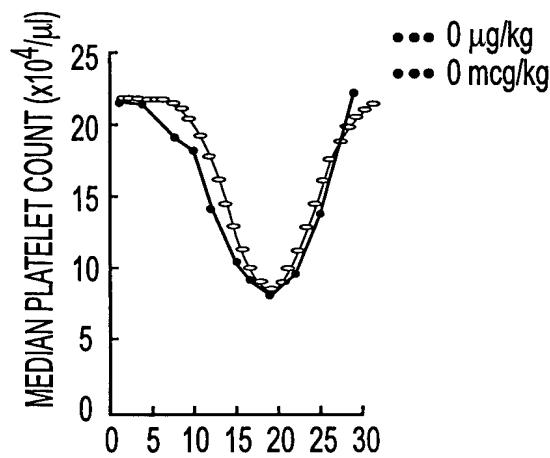


FIG. 9A

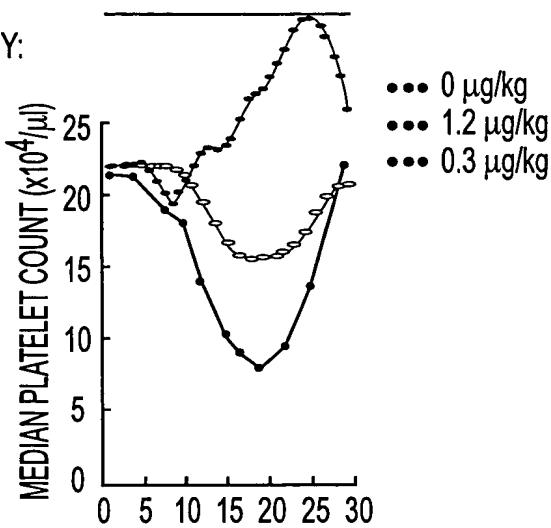


FIG. 9B

FIG. 9: TPO WITH CHEMOTHERAPY- (A) RESULTS OF CLINICAL TRIALS FROM RECENT RESEARCH ON THROMBOCYTOPENIA INDUCED IN PATIENTS RECEIVING SINGLE CARBOPLATIN CHEMOTHERAPY<sup>2</sup> DAY 0 (BLACK), AS COMPARED TO OUR MODEL SIMULATION OF THESE RESULTS (GREEN). (B) THE SAME EXPERIMENTAL DATA (BLACK); SIMULATIONS OF THE SAME EXPERIMENT, WITH ADDITION OF "CONVENTIONAL" TPO PROTOCOL OF A SINGLE IV DOSE OF 1.2  $\mu$ g/kg ON DAY 0 (OLIVE); SIMULATIONS OF THE SAME EXPERIMENT UNDER OUR PROPOSED PROTOCOL THAT TOTALS 0.3  $\mu$ g/kg (BLUE).

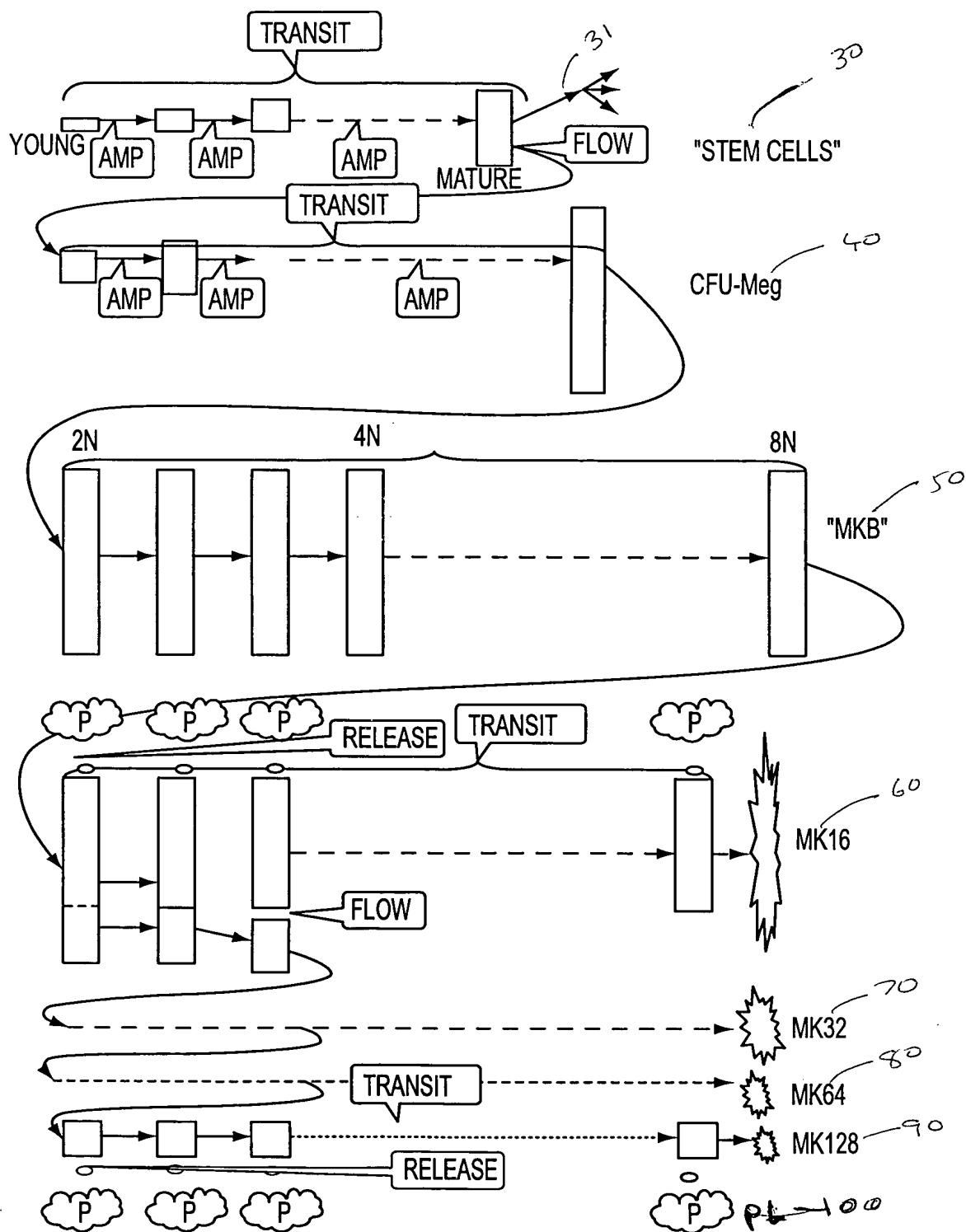


FIG. 3